PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference IB/G -33166A/BCK	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2004/003988	International filing date *(day/month/year)* 15 April 2004 (15.04.2004)	Priority date *(day/month/year)* 16 April 2003 (16.04.2003)]
International Patent Classification (IPC) or national classification and IPC [7] C07D 501/06, 501/44		
Applicant SANDOZ AG		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 21 October 2005 (21.10.2005)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Authorized officer Yolaine Cussac Telephone No. +41 22 338 70 80

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/003988	15.04.2004	16.04.2003

International Patent Classification (IPC) or both national classification and IPC
C07D501/06, C07D501/44

Applicant
SANDOZ GMBH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer
Grassi, D
Telephone No. +49 89 2399-8499

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-18
	No: Claims	
Inventive step (IS)	Yes: Claims	1-18
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-18
	No: Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

D1: EP0531981
D2: US 6 384 215
D3: US 2002/156272
D4: EP0137440
D5: Database CASREACT: accession no. 140:111151
D6: US 5 574 154

Re Item IV

The present application contains four inventions not being linked by a general inventive concept.

D1 discloses the preparation of Cefepime Dihydrochloride Monohydrate (cf. example 31).

The technical problem underlying the present claims is seen in the provision of alternative processes for the preparation of Cefepime Dihydrochloride Monohydrate.

The only technical feature common to the present process claims is the structure of Cefepime Dihydrochloride Monohydrate. In view of D1, the said feature can not establish unity among the different process claims.

Consequently, the following groups of inventions can be distinguished.

1. Claims 1-9
   Process for the preparation of Cefepime Dihydrochloride Monohydrate via intermediate V and the intermediate.

2. Claims 10-13
   Process for the preparation of Cefepime Dihydrochloride Monohydrate via intermediate VIII.

3. Claim 14-18
   Process for the preparation of Cefepime Dihydrochloride Monohydrate applying the reagent XII.

Furthermore, the first invention as mentioned above is still not unitary.

The technical problem underlying the present claims 1-4 is seen in the provision of an alternative process for the preparation of Cefepime Dihydrochloride Monohydrate (known from D1).

The document D2 generically relates to the preparation cephalosporins (R_2 is a standard cephalosporin substituent) from the reactive thioester (I) and the 7-aminocephem compound (V), followed by treatment of the so obtained intermediate with thiourea (cf. columns 4/5). In the background section of D2 the preparation of Cefepime is explicitly mentioned (cf. column 2).

In view of the disclosure of the documents D1 and D2, the present processes according to claim 1 involving either the starting compound IIA and IIB do not share a common special technical feature as required by Rule 13 PCT.

Consequently, the present claims 1-9 encompass the following two groups of inventions:

1.1. Claims 1-4 (part), 5,6 and 8-9 (part)
Process for the preparation of Cefepime Dihydrochloride Monohydrate starting from compound IIA and the intermediates according to claims 5-9.

1.2. Claims 1-4 and 8-9 (all part)
Process for the preparation of Cefepime Dihydrochloride Monohydrate starting from compound IIB.

Re Item V

First invention (Process for the preparation of Cefepime Dihydrochloride Monohydrate starting from compound IIA and the intermediates according to claims 5-9).

1) D1 represents the closest prior art and discloses the preparation of Cefepime Dihydrochloride Monohydrate (cf. example 31).

The technical problem underlying the present claims 1-9 is seen in the provision of alternative processes for the preparation of Cefepime Dihydrochloride

Monohydrate and intermediates therefore.

The document D2 generically relates to the preparation cephalosporins (R_2 is a standard cephalosporin substituent) from the reactive thioester (I) and the 7-aminocephem compound (V), followed by treatment of the so obtained intermediate with thiourea (cf. columns 4/5). In the background section of D2 the preparation of Cefepime is explicitly mentioned (cf. column 2).

2) The subject-matter of present claims 1-9 is regarded as new selection from the document D2 (Article 33(2) PCT).

3) The subject-matter of claims 1-9 does not involve an inventive step (Article 33(3) PCT).

The subject-matter of claim 1-4, 8 and 9 consists in a selection (preparation of Cefepime Dihydrochloride Monohydrate) from the subject-matter of document D2 (cf. above). Such a selection can only be regarded as inventive, if the selected process presents unexpected effects or properties in relation to the rest of the processes (cf. examples 2-6 of D2). However, no such effects or properties are indicated in the application. Hence, no inventive step is present in the subject-matter of claims 1-4.
The intermediates according to claims 5-7 would only involve inventive activity if the process claims 1-4 fulfilled the said requirement.

Second invention (Process for the preparation of Cefepime Dihydrochloride Monohydrate starting from compound IIB).

D1 represent the closest prior art and discloses the preparation of Cefepime Dihydrochloride Monohydrate (cf. example 31).

The technical problem underlying the present claims 1-4, 8 and 9 is seen in the provision of alternative processes for the preparation of Cefepime Dihydrochloride Monohydrate.

The document D3 relates to the preparation of different cephalosporins of formula I from the compounds of formula IV and II via the desilylated intermediate of formula II

(cf. paragraph [0012]) which is treated with thiourea. D2 explicitly mentions cefepime as preferred compound of formula I (cf. paragraph [0019]).

The subject-matter of claim 1-4, 8 and 9 consists in a selection (preparation of Cefepime Dihydrochloride Monohydrate) from the subject-matter of document D3 (cf. above). Such a selection can only be regarded as inventive, if the selected process presents unexpected effects or properties in relation to the rest of the processes. However, no such effects or properties are indicated in the application. Hence, no inventive step is present in the subject-matter of claims 1-4, 8 and 9.

Third invention (Process for the preparation of Cefepime Dihydrochloride Monohydrate via intermediate VIII).

The subject-matter of claims 10-13 does not involve an inventive step (Article 33(3) PCT).

D4 represent the closest prior art for claims 10-13 and generically discloses the preparation of cephalosporin derivatives as Cefepime (cf. claim 1, pages 6-8 and examples 2-4, 10-12, 20, 21, 25, 27, 44, 46, 50, 53). The said process involves the reaction of the unprotected amino acid II with an amine AH (e.g. N-methylpyrrolidine, cf. examples 44, 50, 53).

The present process differs from the process a) as disclosed on pages 6-8 of D4 in that the final product is Cefepime Dihydrochloride Monohydrate and in that desilylation of present compound VIII is required.

The technical problem underlying the present claims 10-13 is seen in the provision of a processes for the preparation of Cefepime Dihydrochloride Monohydrate.

The document D3 discloses a process for the preparation compound IIIA from IIA (cf. page 5, left-hand column). The said compound IIA is the di-trimethylsilyl protected precursor of compound II of D4. Furthermore the document D3 refers several times to conventional methods of desilylation by treatment with water and/or alcohol (cf. D3 paragraph 31, 44 or 61).

Consequently, the combination of the documents D4 with D3 prompts the skilled in the

art faced with the above mentioned problem to prepare the compound II of D4 from the compound IIIA of D3 (i.e. present compound VIII) by treatment with water and/or alcohol and to react the so obtained compound II of D4 with N-methylpyrrolidine. Thereby, the skilled in the art arrives at the process of present claim 10.

Fourth invention (Process for the preparation of Cefepime Dihydrochloride Monohydrate applying the reagent XII).

D5 represents the closest prior art for claims 14-18 and discloses the preparation of Cefepime Dihydrochloride Monohydrate (compound C) from A and B in the presence of NEt3 in a yield of 67% (cf. CASREACT abstract, RX(1)). In view of the fact that the starting compound A is the mono-hydrochloride salt and that the end product is the di-hydrochloride salt, it can be assumed that the process of D5 involves the precipitation with HCl.
The CASREACT abstract of the originally Chinese document does not disclose the solvent used.

In order to finalise the novelty and inventive step assessment of the present claims 14-18 a translation of the original document (Gong. P. et al., HONGGUO YAOWU HUAXUE ZAZHI, 2002, 12(6) 350-351, 362) would be required.
For the time being, the claims 14-18 are regarded as formally new over D5. However, the said claims do not involve an inventive step. In order to involve an inventive step, the selection of a specific solvent would have to exhibit unexpected effects or properties

Additionally, the document D6 relating to the preparation of related compounds by using present compound XII, proposes the use of acetone as solvent (cf. Figure 1 and column 3, lines 36-40).